Clinical impact of (18)F-choline PET/CT in patients with recurrent prostate cancer

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Abstract: PURPOSE: To investigate the clinical value of (18)F-fluorocholine PET/CT (CH-PET/CT) in treatment decisions in patients with recurrent prostate cancer (rPCA). METHODS: The study was a retrospective evaluation of 156 patients with rPCA and CH-PET/CT for restaging. Questionnaires for each examination were sent to the referring physicians 14-64 months after examination. Questions included information regarding initial extent of disease, curative first-line treatment, and the treatment plan before and after CH-PET/CT. Additionally, PSA values at diagnosis, after initial treatment, before CH-PET/CT and at the end of follow-up were also obtained from the questionnaires. RESULTS: Mean follow-up was 42 months. The mean Gleason score was 6.9 at initial diagnosis. Initial treatment was: radical prostatectomy in 110 patients, radiotherapy in 39, and combined prostatectomy and radiotherapy in 7. Median PSA values before CH-PET/CT and at the end of follow-up were 3.40 ng/ml and 0.91 ng/ml. PSA levels remained stable, decreased or were below measurable levels in 108 patients. PSA levels increased in 48 patients. In 75 of the 156 patients (48%) the treatment plan was changed due to the CH-PET/CT findings. In 33 patients the therapeutic plan was changed from palliative treatment to treatment with curative intent. In 15 patients treatment was changed from curative to palliative. In 8 patients treatment was changed from curative to another strategy and in 2 patients from one palliative strategy to another. In 17 patients the treatment plan was adapted. CONCLUSION: CH-PET/CT has an important impact on the therapeutic strategy in patients with rPCA and can help to determine an appropriate treatment.

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Clinical impact of 18F-Choline PET/CT in patients with recurrent prostate cancer

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ABSTRACT

Purpose: To investigate the clinical value of 18F-Fluorocholine PET/CT (CH-PET/CT) regarding treatment decisions in patients with recurrent prostate cancer (rPCA).

Methods: Retrospective evaluation of 156 patients with rPCA and CH-PET/CT for re-staging. Questionnaires for each examination were sent to the referring physicians 14-64 months after examination. Questions included information regarding initial extent of disease, curative first-line treatment, as well as the treatment plan before and after CH-PET/CT. Additionally, PSA values were collected from the questionnaire at diagnosis, after initial treatment, before CH-PET/CT and at the end of follow-up.

Results: Mean follow-up was 42 months; mean Gleason Score was 6.9 at initial diagnosis. Initial treatment was: Radical prostatectomy (n=110), radiotherapy (n=39), combined prostatectomy and radiotherapy (n=7). Median PSA values before CH-PET/CT and at end of follow-up were 3.40 ng/ml and 0.91 ng/ml. PSA levels remained stable, dropped or were below measurable levels in 108 patients. PSA levels rose in 48 patients. In 75/156 patients (48%) treatment plan changed due to findings in CH-PET/CT. In 33 patients the therapeutic modality changed from a palliative to a curative intended treatment. In 15 patients the therapeutic modality was altered from a curative towards a palliative setting. 8 patients had a change from one curative modality to another and 2 patients from one palliative modality to another. 17 patients had adaptations within their therapeutic modality.

Conclusion: CH-PET/CT has an important impact on therapeutic strategy in patients with recurrent prostate cancer and can help to determine an appropriate treatment.

INTRODUCTION

Adenocarcinoma of the prostate (PCA) is the most common malignant tumor in men in the United States of America with second-most cancer-deaths per year following bronchial carcinoma [1]. Nevertheless current staging and re-staging procedures especially regarding nodal involvement and distant metastases still have many limitations leading to insufficiencies in curatively intended therapies. Consequently as many as 19-53 % of treated patients with initially curative intention suffer from recurrent disease [2-5]. Rising levels of prostate specific antigen (PSA) in the blood serum of patients indicate tumor progression often long before imaging modalities can detect any abnormalities. In this biochemical relapse situation there are no guidelines giving any conclusive suggestions regarding imaging procedures. Bone-scintigraphy and CT are both insensitive and show reliable results only at PSA levels of above 20 ng/ml [6]. Thus according to the current guidelines these examinations can safely be omitted. Depending solely on the kinetics of the rising PSA levels the decision is made whether a local recurrence or a distant recurrence is present. If a local recurrence is suspected patients may qualify for a salvage procedure of the prostate fossa. If distant disease is suspected only palliative antihormonal treatment is suggested. MRI with endorectal coil shows reliable results in the evaluation of the prostate fossa but is not routinely recommended by the guidelines [6-8]. 18F-Choline PET/CT (CH-PET/CT) is a promising examination tool for the detection of recurrent prostate cancer (rPCA) [9]. Even though the exact role of the examination is still being discussed it seems that CH-PET/CT starts playing a role in the management of patients with a biochemical relapse [10] [11]. Several studies have demonstrated that CH-PET/CT either labeled with C-11 [12] [13] or with F-18 [14] [15] can detect tumor recurrence at PSA levels of above 2ng/ml giving the clinicians the opportunity of a curative intended salvage procedure at an early time-point of the recurrence [12-15].

In certain constellations tumor recurrence can even be detected if PSA levels are below the level of 2ng/ml, however the detection rates drop in these patient populations down to approx. 30-40% [13] [16]. Even though localized treatment of distant metastases currently is not an established therapy several reports have already been published, showing promising results regarding CH-PET/CT guided radiation therapy and salvage surgery [17-19]. We therefore retrospectively analyzed the impact of the results of CH-PET/CT examinations performed at our institution on treatment decisions.

MATERIALS AND METHODS

This study was conducted according to the local-ethics committee guidelines for retrospective analyses. Between March 2003 and October 2007 we performed 353 CH-PET/CT examinations in patients with PCA. Of these patients 229 had had rising PSA levels after an initial treatment with surgery, radiation therapy or both, indicating recurrent disease. Since no recommendations were given by the guidelines previous conventional imaging (e.g. bone-scan, MRI, CT) was not required for inclusion into our follow-up study [6-8]. Questionnaires were created and sent to the referring physicians in December 2008, 14 months after the scan of the last included patient. After a waiting period of approximately 4 weeks those physicians who had not returned the questionnaires were once reminded by telephone.

CH-PET/CT

All the data were acquired on a combined PET/CT in-line system (Discovery LS or Discovery ST, GE Health Systems, Milwaukee, WI). These dedicated systems integrate a PET scanner (GE Advance Nxi, GE Health Systems, Milwaukee, WI) with a multislice helical CT (LightSpeed plus or LightSpeed 16; GE Health Systems, Milwaukee, WI) and permit the acquisition of co-registered CT and PET images in one session. No oral or intravenous CT contrast agent was used. Patients were examined in the supine position. The unenhanced CT scans were acquired with the following parameters: 80 mA, 140 kV, 0.5-second tube rotation, 4.25 mm section thickness, 867 mm scan length, and 22.5 second data acquisition time. The CT scans were acquired during breath hold with the normal expiration position, and scanning included the area from the head to the pelvic floor. The PET emission scan started 3-4 minutes after the injection of a standard dose of 200-300 MBq 18F-Fluorocholine. After the acquisition of a partial-body scan (pelvic floor to vertex)

approx. 15-20 min post-injection a second partial-body scan with same scan-length was acquired, without taking the patient off the examination-table and without voiding of the bladder. The PET images were acquired starting at the level of the pelvis, with an acquisition time of 3 minutes for the emission scan per cradle position and a one-slice overlap. The CT data were used for attenuation correction, and images were reconstructed using a standard 2D-iterative algorithm (ordered subset expectation maximization).

For image fusion, 4.25 mm thick CT image-slices were reconstructed. Images were then transferred to a commercially available workstation (GE Advantage Workstation). These workstations allow simultaneous data evaluation of early and late phase PET studies with the corespondig CT images as a single procedure and in an image fusion mode.

Both partial-body PET scans were fused with the CT-scan and read side by side. The early scan was primarily used for the evaluation of the prostate fossa because at this time the tracer hasn't arrived in the bladder. The late scan was used for better differentiation between reactive / Inflammatory and malignant lymph nodes [20]. A visually detectable washout of the tracer from lymph nodes over time was considered as benign whereas a persisting or increasing tracer-activity in lymph nodes was considered as a sign for malignancy.

Diagnostic Findings

All CH-PET/CT examinations were reported by a dual-board-certified radiologist / nuclear medicine physician with 5 years of experience in CH-PET/CT reading. The findings from each CH-PET/CT examination were collected from these written reports. Although performed in some patients a validation of the findings from CH-PET/CT with other imaging methods or with a histological workup could not be

obtained consistently due to the retrospective character of the study and was therefore not required for inclusion into the study-population.

Questionnaire:

The questionnaire consisted of questions regarding the following topics:

1) Initial TNM – stage and initial grading according to Gleason
2) Initial therapies and antihormonal treatments
3) Treatment after CH-PET/CT and hypothetical treatment if no CH-PET/CT had been available.
4) PSA values at diagnosis, after initial therapy, before CH-PET/CT and at the end of follow-up.

The referring physicians had to indicate the therapeutic strategy of the patient as it had been defined after the results from CH-PET/CT. Then they had to define a hypothetical therapeutic strategy, assuming the results from the CH-PET/CT had not been available. Additionally they had to indicate whether the effectively chosen treatment plan had been influenced by the CH-PET/CT **(Table 2).** A change in therapy consisted of the choice of a different therapeutic modality (e.g. antihormonal therapy → radiation therapy) or of an alteration within a therapeutic modality (e.g. adaptation of the radiation field)

Statistical data analysis:

General descriptive statistics were performed to calculate mean age, mean follow-up and median PSA-values. Due to the substantial skew of the PSA value distribution a logarithmic transformation was performed for all PSA values to obtain a symmetric distribution. A constant value of 0.01 was added to all PSA values before transformation to make PSA values of zero valid for transformation. PSA

development-ratios from PSA values before and after CH-PET/CT were calculated by subtracting the log transformed post-CH-PET/CT values from the log transformed pre-CH-PET/CT values. Non-parametric testing (Mann-Whitney U Test) was used for comparison of PSA development-ratios among different patient subgroups. The Wilcoxon signed rank test was used for comparison of PSA values before and after CH-PET/CT. P-values < 0.05 were considered significant. All statistical analyses were performed using SPSS for Windows, Release 18.0.0 (SPSS Inc., Chicago, IL)

RESULTS

Disease characteristics

A total of 163 questionnaires could be obtained by the referring physicians. 7 patients with returned questionnaires had to be excluded because of missing PSA values before CH-PET/CT and/or at the end of follow-up. Finally 156/229 (68%) completed questionnaires could be used for evaluation (Table 1). Mean follow-up was 42 months (range 14 – 64 months). Mean age of the patients at the time of CH-PET/CT was 66 years (range 48 – 81 years). At diagnosis the mostly represented tumor stage was T3 N0 M0 with a mean Gleason Score of 6.91 **(Table 2)**. Initial treatment consisted of radical prostatectomy in 110 patients. 39 patients had undergone radiotherapy and 7 patients a combination of both.

Diagnostic performance

Positive findings in CH-PET/CT were reported in 124/156 (79%) patients. 63/156 (40%) patients had a local recurrence only, 27/156 (17%) patients had lymphatic metastases only and 9/156 (6%) patients had metastases to the bones only. A local recurrence plus nodal metastases were found in 14/156 (8%) patients and 8/156 (5%) of patients had local recurrence plus bony metastases. 4/156 (3%) of patients had tumor manifestations in the prostate fossa, in lymph nodes and in the bones.

Effective vs. hypothetical treatment

In 75/156 patients (48%) the referring physicians indicated a change of the therapeutic strategy. In 33 patients (21%) the therapeutic modality changed from a palliative to a curative intended treatment (surgery, radiation therapy, HIFU and combined therapies). In 15 patients (10%) the therapeutic modality was altered from

a curative towards a palliative setting (watchful waiting, antihormonal treatment or chemotherapy). 8 patients (5%) had a change from one curative modality to another and 2 patients (1%) from one palliative modality to another. 17 patients (11%) had adaptations within their therapeutic modality **(Tables 2 and 3)**. In 8 patients (6%) a change in therapy was indicated even though CH-PET/CT showed no abnormities. Three of these patients (initially operated) scheduled for RT before CH-PET/CT had an adaptation of their radiation field. One patient (initially operated) was changed from RT to surgery. One patient (initially operated) scheduled for surgery had an adaptation of his surgical procedure. One patient (initially operated) scheduled for RT and additional antihormonal treatment was changed to antihormonal treatment only. One patient (initially with RT) was changed from antihormonal treatment to watchful waiting. One patient (initially operated) scheduled for antihormonal treatment had an adaptation of this treatment.

PSA values

Table 4 summarizes the PSA values of our patient population at the different time-points. Since 2 patients had extraordinarily high PSA values at the end of follow-up (One patient had a PSA of 150 ng/ml and the other 334.8 ng/ml) not only mean PSA levels but also median values were calculated to correct for the overwhelming influence of these two patients on the results. PSA levels before CH-PET/CT were significantly higher compared to those at the end of follow-up ($P < 0.001$; Wilcoxon signed rank test). At the end of follow-up, PSA values declined in 107 patients (69%) due to subsequent therapies. Of these 107 patients 16 (10%) had values below the measurable threshold. 1 patient (1%) had a stable PSA and in 48 patients (31%) the PSA levels increased.

PSA values before CH-PET/CT were significantly higher ($P < 0.001$, Mann-Whitney U Test) in patients with positive CH-PET/CT scans (median PSA 4.50 ng/ml, range 0.15 - 296.61 ng/ml) compared to those with negative scans (median PSA 1.20 ng/ml, range 0.1 - 30.3 ng/ml). However there was no significant difference regarding the PSA development-ratios (obtained from the PSA-values before and after CH-PET/CT) in the comparison of patients with positive CH-PET/CT to those with negative scans ($P = 0.70$, Mann-Whitney U Test). These two groups did not differ regarding initial PSA levels at the time point of diagnosis ($P = 0.48$, Mann-Whitney U Test).

PSA values of the patients where the intended treatment plan was changed after CH-PET/CT (n=75, 48%) were compared with those of patients where no change of treatment had been performed (n=81, 52%). There was no significant difference between these two groups regarding the PSA development-ratios (pre-/post CH-PET/CT) ($P = 0.68$, Mann-Whitney U Test). Again the PSA values at the time of primary diagnosis were not significantly different in these two groups ($P = 0.67$, Mann-Whitney U Test)

DISCUSSION

To our knowledge this retrospective analysis is the first, to analyze the clinical impact of CH-PET/CT on treatment decisions in patients with recurrent prostate cancer. We obtained our data using questionnaires, which were sent to those physicians who had referred their patients for a CH-PET/CT to our institution. The referring physicians had to provide information about the therapy, which had been performed after CH-PET/CT and had to determine a hypothetical therapeutic management without the information obtained from the CH-PET/CT. With this method we could demonstrate a strong clinical impact of CH-PET/CT. The results of our examination lead to changes of the therapy in 48% of patients, which consisted of adaptation of the current treatment-regime or even complete change of the therapeutic approach. Even though a comparison with a non-CH-PET/CT control group was not possible due to the retrospective study design, the performed therapies after CH-PET/CT were effective since a significant decline of the mean PSA values after the examination compared to before could be observed.

Interestingly PSA development-ratios of patients with positive findings in CH-PET/CT compared to those with negative findings demonstrated no statistical significance. The same accounted for the comparison of patients with therapeutic changes due to CH-PET/CT compared to those without. We believe that there are several factors, which lead to these results:

If patients had no findings in CH-PET/CT the treatment in general followed the standard procedures for recurrent disease [6-8]. According to the guidelines in such a situation if no other findings are present the decision whether a local or distant recurrence is present is made by the PSA kinetics. The standard procedures then are radiation therapy (if initially undergone surgery), antihormonal treatment, salvage resection, or combined approaches. After such a procedure the likelihood of a

successful treatment is high, especially since CH-PET/CT (even though per definition false negative due to rising PSA) has excluded gross metastatic spread. Thus it is not surprising that not only those of our patients with positive findings in CH-PET/CT had favourable PSA development-ratios but also those without detectable pathologies in the CH-PET/CT examination.

The situation with the subgroup of patients with therapeutic changes compared to those without is quite similar. If CH-PET/CT confirmed the suspected localization of recurrent disease no change of therapy management occurred. The intended treatment-approach remained correctly unchanged for these patients and the PSA development-ratios were of course as favourable as they were for those patients where CH-PET/CT demonstrated findings which led to a change of the therapeutic management.

Therefore, it becomes clear that with our study setup it is not possible to make statements about the influence of CH-PET/CT on the outcome of recurrent prostate cancer.

Interestingly in 8 patients the referring physicians indicated changes in therapy even though CH-PET/CT demonstrated no positive findings. These results can be explained by the fact that despite the failure to detect the recurrent disease CH-PET/CT was able to exclude gross metastatic spread. This obviously led to changes of the planned treatment such as adaptation of the radiation field.

The major limitation of our study is its retrospective character. Our referring physicians had to retrospectively determine which therapy would have been performed if no CH-PET/CT had been available. There is potential bias, since the referring physicians were most likely to support CH-PET/CT. Thus more favourable results regarding therapeutic changes could be assumed compared to a real prospective study design. Nevertheless we believe that no serious bias has been

introduced into our study. First of all, according to the guidelines for prostate cancer recurrence the therapeutic options are not very wide. They consist of radiation therapy, antihormonal treatment, salvage surgery, chemotherapy or a combination of these. There were two categories of patients referred for CH-PET/CT. The first category consisted of patients who had had a complete treatment with initial curative therapy, recurrence, salvage procedure and again rising PSA levels. Following the guidelines in such a situation without further diagnostics only a palliative procedure with antihormonal treatment or watchful-waiting was advised. Any therapy aside these two options was therefore very likely to be due to CH-PET/CT and a bias was basically only possible if a change of therapy occurred within the two palliative options, which was indicated in only 2/75 patients. The second category were patients whose PSA didn't decline sufficiently or started rising again after initial curative therapy. For these potentially curable patients the standard procedure according to the guidelines is a salvage locoregional therapy mostly consisting of surgery or radiation therapy. Thus indicated therapeutic changes from a curative to a palliative setting (15/75 patients) or within the same curative modality, like extended lymphadenectomy or extended radiation field (16/75 patients), were most likely correct and not due to a bias. The only potential for biasing was given in those patients where therapeutic changes were indicated from one curative setting to another (8/75 patients).

Conclusion

According to the results in our patient population CH-PET/CT in patients with recurrent prostate cancer has an important impact on the therapeutic strategy and can help to determine an appropriate treatment for these patients.

Conflict of Interest statement

All authors declare that they have no conflict of interest.

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TABLES

Table 1

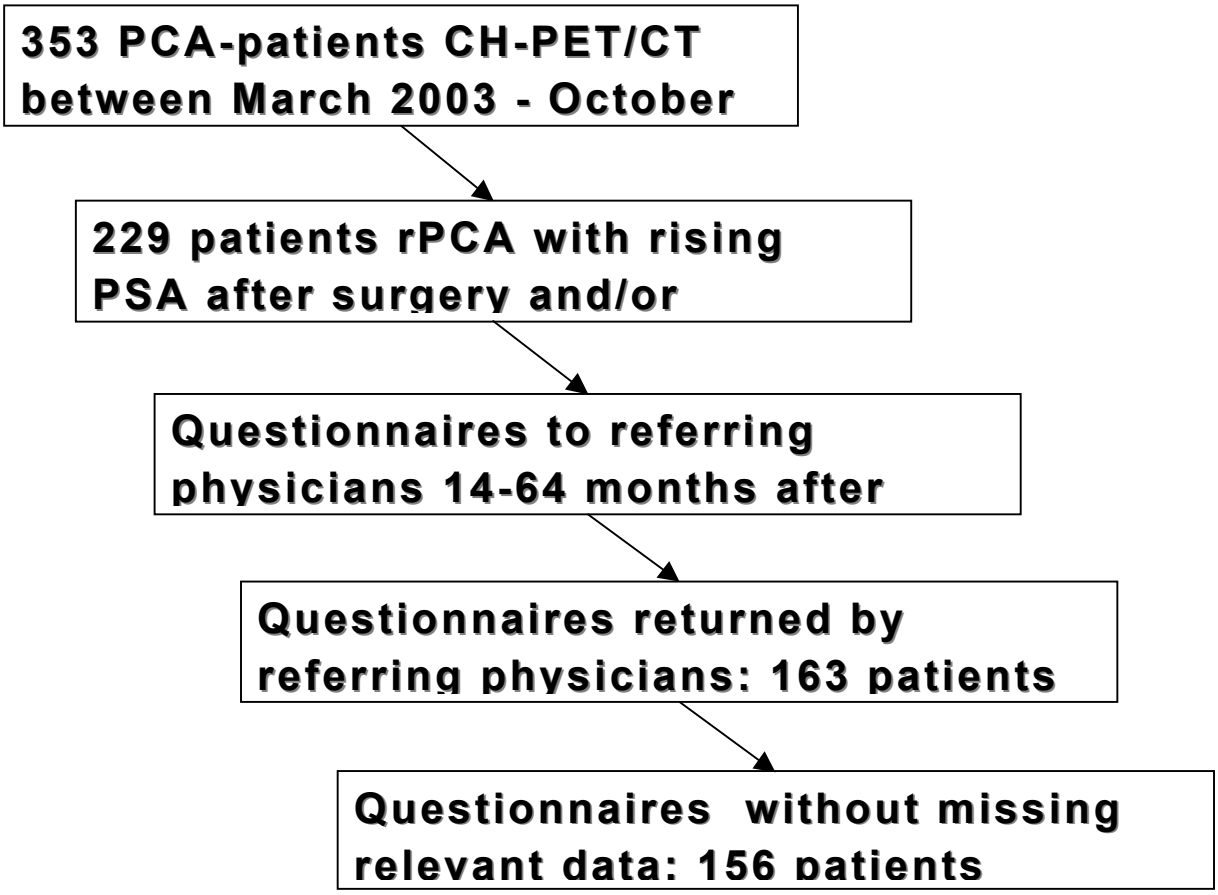


Table 1 describes our patient inclusion-pathway.

Table 2

Table 2A

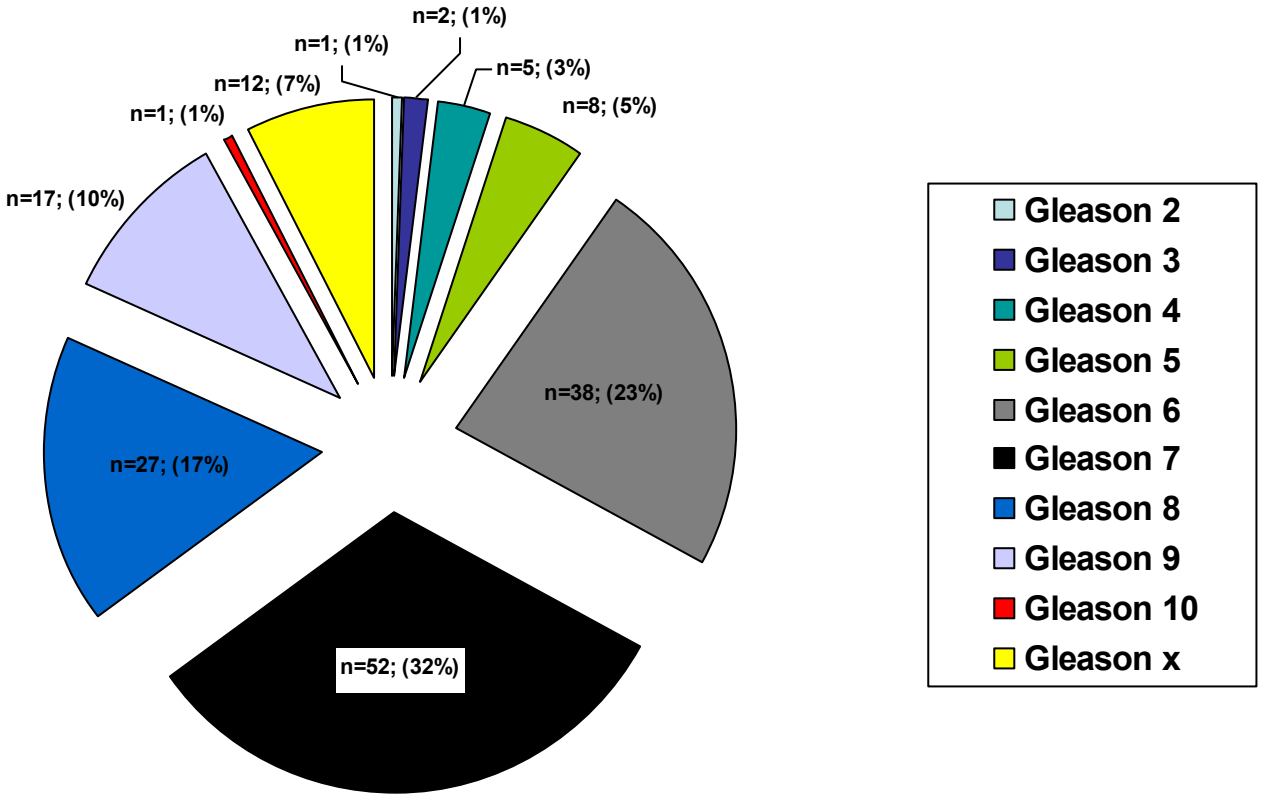


Table 2B

TNM-Stage	N0	N1	Nx	M1
T1	14	0	0	0
T2	52	5	6	0
T3	61	6	6	3
T4	2	2	1	2
TX	0	0	1	0

Table 2 shows the disease characteristics of our patient population. In table 2A the distribution of Gleason Scores is visualized. Table 2B shows the TNM stages of our patients. For an easier understanding patients with MX were treated as M0 in this table. 5 patients had distant metastases (3 patients T3 N1 M1; 1 patient T4 N0 M1 and 1 patient T4 NX M1)..

Table 3

	Watchful waiting (no therapy)	Antihormonal treatment	Radiation therapy	Surgery	HIFU	Chemotherapy	Anthormonal and radiation therapy	Surgery and radiation therapy
Therapy with CH-PET/CT	19	37	59	11	6	1	22	1
Hypothetical therapy without CH-PET/CT	22	54	60	4	2	0	14	0

Table 3 shows the effectively performed treatments with CH-PET/CT in the upper column and the hypothetical treatments without CH-PET/CT as indicated by the referring physicians in the lower column.

Table 4

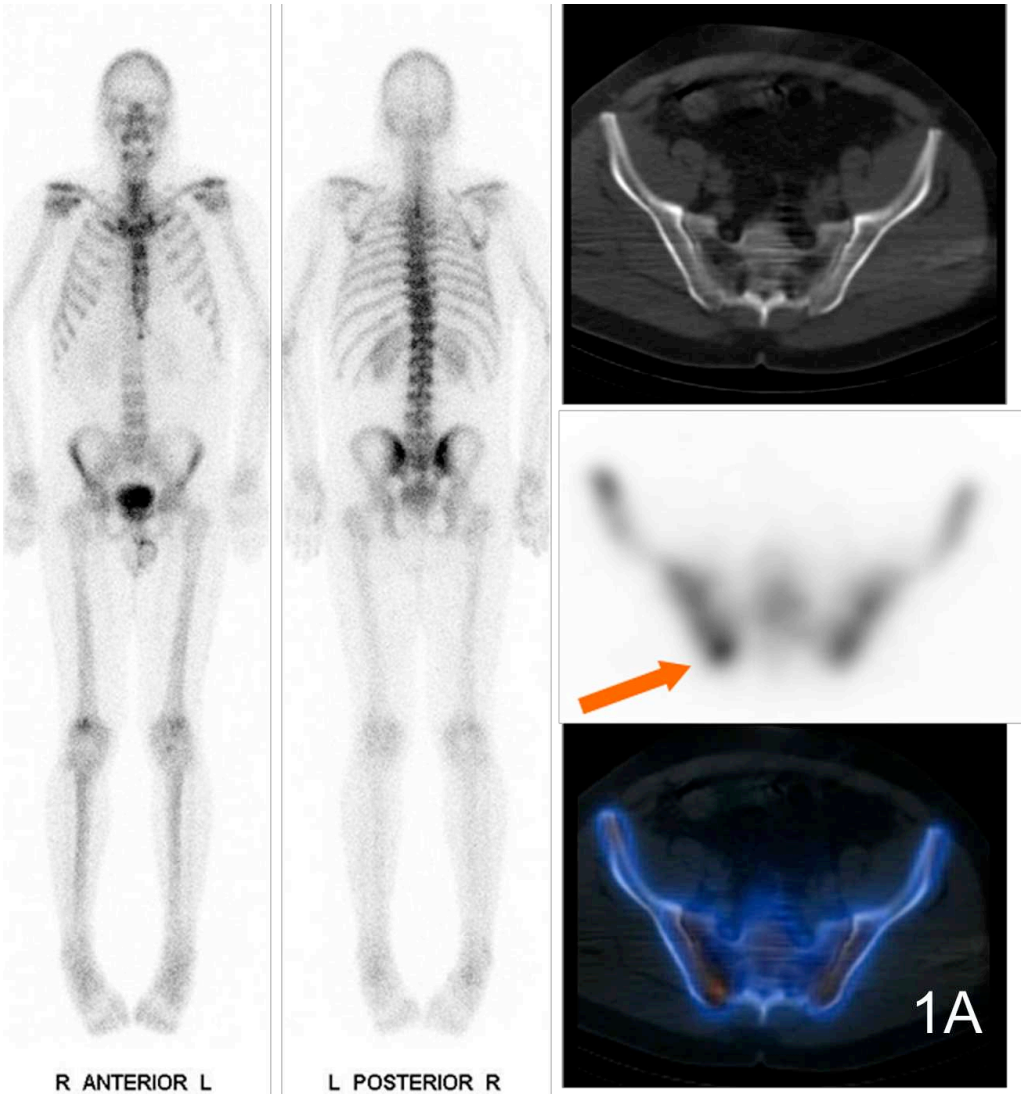
PSA	At diagnosis	Nadir after treatment	Before CH-PET/CT	At end of follow-up
Available in n=	149/156	139/156	156/156	156/156
Mean value ng/ml	22.18	0.72	9.46	9.50
Median value ng/ml	12.00	0.10	3.40	0.91

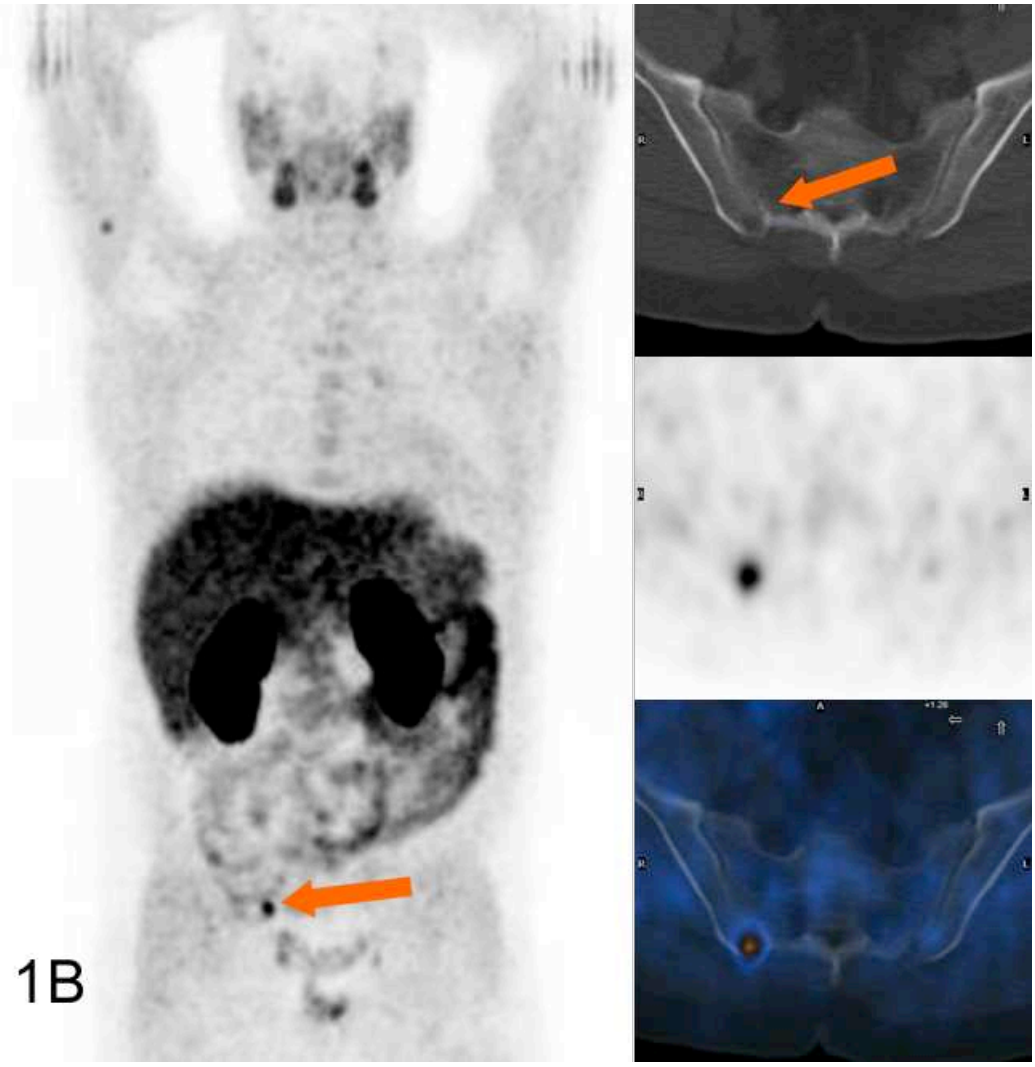
Table 4 describes the PSA values of our patients (including the availiability of the measurements) at selected time-points.

FIGURES

Figure 1

53 year old patient, 6 years after surgery. Rising PSA 3.0 ng/ml. Bone scintigraphy including SPECT/CT was read as negative, also in the right iliac bone (arrow) (1A). Thus a local recurrence was suspected leading to a hypothetical treatment with radiation therapy of the small pelvis. CH-PET/CT performed 4 weeks later revealed a metastasis in the iliac bone (1B). The therapy-management was changed to a radiation therapy of the iliac bone and additional antihormonal treatment. PSA declined to 2.45ng/ml





1B

Figure 2

74 year-old patient, 3 years after surgery. Rising PSA 2.2 ng/ml. CH-PET/CT confirmed a clinically suspected local recurrence. No change in therapy-management. Patient received radiation therapy and PSA declined to 0.43 ng/ml